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False Prolongation of Activated Partial Thromboplastin Time with Aminoglycoside Antimicrobial Agents: A Case Report

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Abstract

BACKGROUND: Activated partial thromboplastin time (APTT) is a clotting time assay for screening bleeding tendency, evaluating coagulation factor production capacity, assessing preoperatively, monitoring anticoagulant drugs, and searching for blood coagulation abnormalities such as hemophilia and antiphospholipid syndrome.

CASE PRESENTATION: Here, we present a 77-year-old male patient with dyspnea who was suspected to have a drug-resistant Pseudomonas aeruginosa infection and pulmonary mycosis. The patient had no history of bleeding tendencies or anticoagulant medication use. The laboratory test results revealed an abnormally prolonged activated partial thromboplastin time (APTT) of 120.3 s using the Coagpia® APTT-N reagent. The APTT test is frequently used to evaluate blood clotting function and assess for bleeding disorders. Prolonged APTT can indicate coagulation factor deficiencies or the presence of certain conditions such as von Willebr and disease, hemophilia, and disseminated intravascular syndrome. However, APTT standardization has not been achieved, causing discrepancies in test results due to variations in the reagents used. The prolonged APTT, in this case, was initially suspected to be caused by contamination or other artifacts, but repeat blood collections and cross-mixing tests revealed the Coagpia® APTT-N reagent as the cause of false prolongation. The reagent was changed to HemosIL SynthASil APTT, which revealed a normal APTT result. The patient had been receiving the aminoglycoside antimicrobial agent tobramycin, and the blood sample taken at the peak tobramycin level demonstrated the longest APTT time. The APTT shortened over time, corresponding to the decrease in tobramycin blood levels.

CONCLUSION: Overall, this paper reports a case of false APTT prolongation due to a specific APTT reagent in the presence of aminoglycoside antimicrobial agents. The findings underscore the difficulties in standardizing APTT testing and the importance of considering reagent performance characteristics in result interpretations.

Introduction

Activated partial thromboplastin time (APTT) is one of the most frequently measured blood coagulation screening tests along with prothrombin time (PT), which are used to assess blood clotting function in patients [1], [2]. APTT is a clotting time assay for screening bleeding tendency, evaluating coagulation factor production capacity, assessing preoperatively, monitoring anticoagulant drugs, and searching for blood coagulation abnormalities such as hemophilia and antiphospholipid syndrome [3], [4], [5], [6].

Prolonged APTT indicates decreased or inactive coagulation factors, von Willebrand factor [7], prekallikrein [8], decreased activity of high molecular weight kininogen [9], and the presence of a lupus anticoagulant (LA) [10], [11]. Specific diseases and conditions include von Willebrand disease, hemophilia, disseminated intravascular syndrome, and Vitamin K deficiency [12], [13]. APTT test consists of two steps. The first step is preincubating the plasma sample with a negatively charged substance (Kaolin, ellagic acid, etc.) to activate Factors XI and XII. The second step starts with calcium ions in the reagent, which trigger a chain of calcium-dependent enzymatic reactions to coagulate fibrinogen (Fib) clotting [14]. Standardization has progressed in PT testing, using the international sensitivity index (ISI) and the ISI to express PT results on a common scale, such as the international normalized ratio (INR) [15]. In contrast, APTT has not been standardized, causing discrepancies in test results even when evaluating the same samples, primarily due to variations in the reagents used. This inconsistency arises from the differential coagulation factor responsiveness and the varying vulnerability to antiphospholipid antibodies and heparin, which are contingent on the specific activator for contact factors and the phospholipid composition within the utilized reagent [16], [17], [18].

We use Coagpia® APTT-N (Sekisui Medical Co., Ltd.) for APTT measurement at our hospital

although it has been previously mentioned that APTT is difficult to standardize due to the variability in reported values depending on the reagent used. The present study reports a false APTT prolongation due to aminoglycoside antimicrobial agents, depending on the APTT reagent composition.

Case Report

A 77-year-old male patient with a chief complaint is dyspnea had chronic bronchitis and interstitial pneumonia and recurrent *Pseudomonas aeruginosa* pneumonia in the context of interstitial pneumonia. A sputum culture test revealed *P. aeruginosa*. The patient was suspected to have a two-drug-resistant *P. aeruginosa* infection and pulmonary mycosis and was admitted to our hospital. The patient had no history of antiplatelet or anticoagulant medications and had no bleeding tendencies.

Laboratory data for year X: Total protein (TP): 4.8 g/dL, albumin (Alb): 1.8 g/dL, C-reactive protein (CRP): 6.21 mg/dL, white blood cell count: 13 × 10^3/μL, red blood cell count: 2.09 × 10^6/μL, hemoglobin concentration: 5.9 g/dL, platelet count: 17.0 × 10^4/μL, PT activity: 100%, PT-INR: 1.00, APTT: 120.3 s, Fib: 341 mg/dL, and antithrombin (AT) activity: 55% (Table 1). The APTT reagent was Coagpia® APTT-N (Sekisui Medical Company, Tokyo, Japan) and was measured with an automated analyzer (CP3000™, Sekisui Medical Company, Tokyo, Japan). The blood draw at 15:00 revealed an abnormally prolonged APTT of 120.3 s, as previously presented. We assessed the collection status with the ward, suspected transfusion contamination, and requested a repeat blood collection. The APTT result of the re-collected blood, which was submitted 1 h after the initial blood collection, was 93.5 s at 16:00. The patient had no bleeding or thrombotic tendencies and the laboratory technician performed another blood collection with the patient's consent to investigate the cause of the prolonged APTT and to exclude artifacts such as heparin contamination. The APTT at 17:30 was 83.3 s, which remains abnormally prolonged. Cross-mixing test was performed with blood collected at 17:30 for unexplained APTT prolongation, and both immediate and delayed reactions after heating at 37°C for 2 h revealed a downward convex pattern of coagulation factor deficiency (Figure 1).

Table 1: Laboratory data

Complete blood count		Biochemistrey		Coagulation	
WBC	12.800/μL	TP	4.8 g/dL	PT	100%
Stab	1.0%	Alb	1.8 g/dL	PT: RATIO	1.00
Seg	93.0%	CRP	6.17 mg/dL	PT: INR	1.00
Lym	1.5%	T-bil	0.4 mg/dL	PT: sec	12.6 s
Mono	4.5%	D-bil	0.2 mg/dL	APTT	120.3 s
RBC	209×10⁴/μL	AST	15 U/L	Fib	341 mg/dL
Hb	5.9 g/dL	ALT	12 U/L	D-dimer	7.7 μg/mL
Hct	18.1%	LD	182 U/L	AT	55%
Plt	17.0×10⁴/μL	ALP	62 U/L		
MCV	87 fL	γ-GT	20 U/L		
MCH	28.2 pg	UN	18.5 mg/dL		
MCHC	32.6%	Cre	0.78 mg/dL		
Retic (‰)	14‰	Na	133 mmol/L		
Retic (×10⁴)	3.5×10⁴/μL	K	3.3 mmol/L		
		Cl	91 mmol/L		
		Ca	7.6 mg/dL		
		Glucose	79 mg/dL		

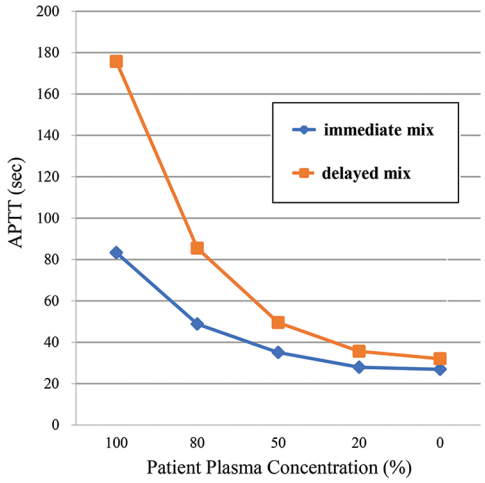
TP: Total protein, Alb: Albumin, CRP: C-reactive protein, WBC: White blood cell count, RBC: Red blood cell count, Hb: Hemoglobin, Fib: Fibrinogen, AT: Antithrombin.

The background of low TP and Alb could be caused by decreased protein synthesis capacity, but the results were contradictory because the PT was normal. The APTT reagent was changed to HemosIL SynthASil APTT (Instrumentation Laboratory, Bedford, MA, US), considering the possibility of contamination by an affected substance, which demonstrated an APTT of 32.2 s, within the normal range. Hence, we suspected that Coagpia® APTT-N was affected by an aminoglycoside antibacterial agent, which is a substance that interferes with Coagpia® APTT-N. We confirmed the patient information and revealed that the aminoglycoside antibacterial agent, tobramycin (TOBRACIN®: TOWA PHARMACEUTICAL CO., LTD.), had been administered. The blood sample with an APTT of 120.3 s had a peak tobramycin value (22.1 μg/mL), while the blood sample taken the next day, which was considered a trough, had a shorter APTT of 44.7 s compared to the previous day. Table 2 shows the identified relationship between the mean of the peak and trough tobramycin concentration and the APTT for 3 weeks before and after the current case.

Discussion

The APTT is one of the most frequent and central components of any screening for hemostatic patency. APTT is used to detect the deficiency of intrinsic clotting factors (VIII, IX, XI, or XII), monitor unfractionated heparin therapy, and evaluate the presence of LA. The major role of APTT at many centers is now the detection of clotting factor deficiencies either in the form of a pre-operative clotting screen or in patients who present with a history of a hemorrhagic diathesis. Some standardization in PT testing has been performed using the ISI or ISI to express PT results on a common scale, such as the INR, as previously mentioned [15]. Conversely, APTT is not standardized and test results vary even when the same specimens are evaluated, mainly due to differences in the reagents used. APTT reagents show different sensitivities to factor VIII, IX, XI, and XII deficiencies. This is thought to be caused by differences in the activator or phospholipids used in the reagent [19], [20].

The cross-mixing test performed in this study is frequently performed in cases of unexplained APTT prolongation and is used to detect hemophilia and LA [21], [22]. LA is one of the three laboratory diagnostic criteria for antiphospholipid antibody syndrome and is an established risk factor for thrombosis [23]. LA can also be transiently detected in patients with underlying



APTT Immediate mix		Delayed mix
Patient plasma ratio, %	Value, sec	Value, sec
100	83.3	175.7
80	48.8	85.4
50	35.0	49.5
20	27.9	35.6
0	26.9	32.0
ICA value	9.7	10.0

Figure 1: Cross-mixing test results. (a) Activated partial thromboplastin time (APTT) cross-mixing test, Cross-mixing test. A five-step dilution cross-mixing test with an amine incorporation assay was performed using the patient's plasma at ratios of 1:0, 4:1, 1:1, 1:4, and 0:1 with normal plasma, : Immediate mix, : Delayed mix (37℃, 2 h), (b) APTT cross-mixing test seconds and ICA values, ICA was calculated as (coagulation time of 50% mixed plasma-coagulation time of normal plasma)/coagulation time of test plasma) × 100. The cutoff value of 12.4 was used, and a value of <12.4 was considered deficient and a value of ≥12.4 was considered non-deficient

Table 2: The relationship between the mean of the peak and trough concentration of tobramycin and the seconds of APTT for the 3 weeks before and after

Timing of blood sample collection	Tobramycin concentration (μg/mL)	APTT (s)
Before administration of Tobramycin	7.1 ± 1.8	44.7
After administration of Tobramycin	22.1 ± 2.9	120.3

APTT: Activated partial thromboplastin time.

malignancies or infections and patients using certain drugs. LA is determined through a functional assay in the laboratory, which shows that a phospholipid-dependent clotting time is prolonged and the prolongation is corrected by adding excessive phospholipid. Persistent LA is a typically acquired risk factor for thrombosis and its identification is very important [24]. The patient, in this case, had no history of taking antiplatelet or anticoagulant medications, had no bleeding tendency, and with coagulation function tests within normal limits in previous blood draws.

Table 3: Activators and phospholipid sources in each APTT reagent

Reagent	Manufacture	Phospholipid	Activator	Calcium chloride solution
Coagpia® APTT-N	Sekisui Medical	Phospholipids from rabbit brain	Ellagic acid	Calcium chloride
HemosIL SynthASil APTT	Instrumentation Laboratory	Synthetic phospholipid	Silica	Calcium chloride

APTT: Activated partial thromboplastin time.

This study confirmed false prolongation only with Coagpia® APTT-N when two types of APTT assay reagents (Coagpia® APTT-N [Sekisui Medical Co., Ltd.] and HemosIL SynthASil APTT [Instrumentation Laboratory, Bedford, MA, US]) were used to measure the same sample. This is thought to be caused by the APTT reagent composition. Table 3 shows the composition of the two APTT reagents used in this case. CRP reacts with phospholipids *in vitro* in cases of high CRP levels, possibly decreasing the amount of phospholipids that react with coagulation factors and prolonging the APTT [1]. Coagpia® APTT-N, which was used in this case, uses phospholipids derived from the rabbit brain as a reagent, and these phospholipids may react with CRP and cause an apparent APTT prolongation. The patient in this case had a CRP of 6.21 mg/dL and the false APTT prolongation by CRP should be considered. Further, concentration-dependent APTT prolongation of aminoglycoside antimicrobial agents has been observed in reagents containing ellagic acid as an activator by administering amikacin sulfate or gentamicin in several APTT reagents. However, aminoglycoside antimicrobial administration in a reagent using silica as an activator (HemosIL SynthASil APTT) hardly prolonged the APTT [25].

The cross-mixing test was performed for the unexplained APTT prolongation, and both the immediate and delayed responses were convex downward, which caused the suspicion of a coagulation factor deficiency. The prolonged APTT was accompanied by a background of low TP and Alb in the patient, indicating decreased protein synthesis capacity, but contradictory results with normal PT. In addition, an interfering substance was suspected based on the change in APTT over time, and a search for antimicrobial use revealed that the patient had received tobramycin (TOBRACIN®: TOWA PHARMACEUTICAL CO., LTD.), which is an aminoglycoside antimicrobial agent. The blood draw with an APTT of 120.3 s had peak tobramycin (TOBRACIN®: TOWA PHARMACEUTICAL CO., LTD.) (22.1 μg/mL), and the shortening of the APTT over time was due to pharmacokinetics.

Tobramycin, which is used in the present case, is an aminoglycoside antibiotic derived from *Streptomyces tenebrarius* and has bacteriostatic activity against aerobic gram-negative bacteria. It is soluble in water and has a molecular weight of 467.5 g/mol. Tobramycin irreversibly binds to the 16S ribosomal RNA of the bacterial 30S ribosomal unit and interferes with the initiation complex between the messenger

RNA and the 30S subunit after being transported into the bacterial cell, thereby inhibiting protein synthesis initiation and resulting in bacterial cell death [26]. A metabolic study of tobramycin in rats revealed a peak blood concentration 10 min after administration, with a blood half-life of 1–2.5 h after injection. The shortening of the APTT over time in tobramycin-treated patients such as the present case may be due to a pharmacokinetics-induced decrease in the blood concentration of tobramycin [27].

This time, with Coagpia® APTT-N (Sekisui Medical Co., Ltd.) reagent, we observed a false APTT prolongation with aminoglycoside antimicrobial agent administration. APTT prolongation has many causes, and we tend to be conscious of searching for pathological conditions, but this case reminded us of the importance of understanding reagent performance characteristics. We would like to increase the number of cases and investigate the relationship between APTT prolongation and blood concentration in the future.

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